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(54) Title: GLYCINE TRANSPORT INHIBITORS

(57) Abstract

The present invention is concerned with the use of glycine transport inhibiting [4,4–bis(4–fluorophenyl)butyl]–1–(piperazinyl and piperidinyl) derivatives for the preparation of medicaments for treating disorders of the central and peripheral nervous system, in particular psychoses, pain, epilepsy, neurodegenerative diseases (Alzheimer's disease), stroke, head trauma, multiple sclerosis and the like. The invention further comprises novel compounds, their preparation and their pharmaceutical forms.

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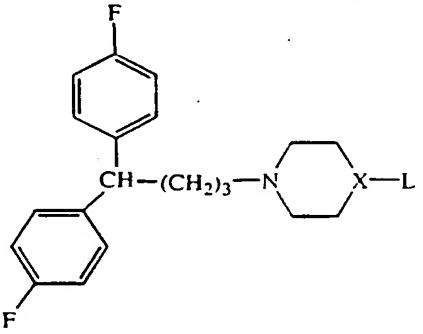
GLYCINE TRANSPORT INHIBITORS

The present invention is concerned with the use of glycine transport inhibiting 4,4-bis-(4-fluorophenyl)butyl]-1-(piperazinyl and piperidinyl) derivatives for the preparation of medicaments for treating disorders of the central and peripheral nervous system, in particular psychoses, pain, epilepsy, neurodegenerative diseases (Alzheimer's disease), stroke, head trauma, multiple sclerosis and the like. The invention further comprises novel compounds, their preparation and their pharmaceutical forms.

4,4-bis(4-fluorophenyl)butyl]-1-(piperazinyl and piperidinyl) derivatives are well-known histamine and serotonine antagonists. These compounds, their activity and preparation were disclosed in EP-A-0,151,826 and GB-1,055,100.

The present invention is concerned with the use of glycine transport inhibiting compounds for the preparation of medicaments for treating disorders of the central and peripheral nervous system, said compounds having the formula

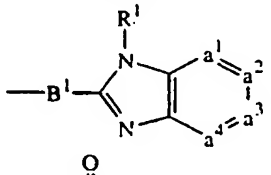


(I)

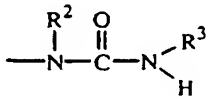
the *N*-oxides, the stereochemically isomeric forms and the pharmaceutically acceptable addition salts thereof, wherein

X represents CH or N;

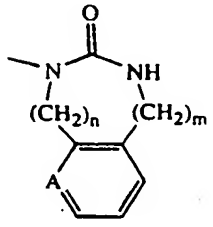
L represents a radical of formula



(a)



(b)



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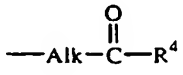


(d)

wherein n is 0 or 1;

m is 0 or 1;

Alk represents C_{1-6}alkanediyl;

A represents N or CH;

B^1 represents CH_2 or NH;

$-a^1=a^2-a^3=a^4-$ represents a bivalent radical of formula

-CH=CH-CH=CH- (a-1); or

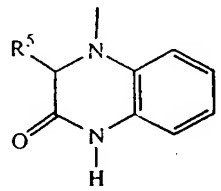
-N=CH-CH=CH- (a-2);

R^1 represents C_{1-4}alkyl optionally substituted with C_{1-4}alkyloxy, pyridinyl, aryl, arylcarbonyl, thienyl, furanyl, imidazo[1,2-a]pyridinyl, thiazolyl;

R^2 represents hydrogen or aryl;

R^3 represents hydrogen, C_{1-6}alkyl or C_{3-7}cycloalkyl;

R^4 represents thienyl, furanyl, arylamino or a radical of formula



(d-1)

wherein R^5 is hydrogen or aryl;

aryl represents phenyl optionally substituted with 1 or 2 substituents selected from C_{1-4}alkyl, halo, hydroxy, C_{1-4}alkyloxy.

The present invention also relates to a method of treating warm-blooded animals suffering from disorders of the central and peripheral nervous system, in particular psychoses, pain, epilepsy, neurodegenerative diseases (Alzheimer's disease), stroke, head trauma, multiple sclerosis and the like. Said method comprises the administration of a therapeutically effective amount of a compound of formula (I) or a *N*-oxide form, a pharmaceutically acceptable acid or base addition salt or a stereochemically isomeric form thereof in admixture with a pharmaceutical carrier.

As used in the foregoing definitions and hereinafter, halo is generic to fluoro, chloro, bromo and iodo; C_{3-7}cycloalkyl is generic to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl; C_{1-4}alkyl defines straight and branched chain saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as, for example, methyl, ethyl, propyl, butyl, 1-methylethyl, 2-methylpropyl, 2,2-dimethylethyl and the like; C_{1-6}alkyl is meant to include C_{1-4}alkyl and the higher homologues thereof having 5 or 6 carbon atoms such as, for example, pentyl, 2-methylbutyl, hexyl, 2-methylpentyl and the like; C_{1-6}alkanediyl defines bivalent straight and branched chain saturated

hydrocarbon radicals having from 1 to 6 carbon atoms such as, for example, 1,1-methanediyl, 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl, 1,5-pentanediyl, 1,6-hexanediyl, 1,2-propanediyl, 2,3-butanediyl and the like.

The pharmaceutically acceptable addition salts as mentioned hereinabove are meant to comprise the therapeutically active non-toxic base and acid addition salt forms which the compounds of formula (I) are able to form. The acid addition salt form of a compound of formula (I) that occurs in its free form as a base can be obtained by treating said free base form with an appropriate acid such as an inorganic acid, for example, hydrohalic acid, e.g. hydrochloric or hydrobromic, sulfuric, nitric, phosphoric and the like acids; or an organic acid, such as, for example, acetic, hydroxyacetic, propanoic, lactic, pyruvic, oxalic, malonic, succinic, maleic, fumaric, malic, tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, *p*-toluenesulfonic, cyclamic, salicylic, *p*-aminosalicylic, pamoic and the like acids.

The compounds of formula (I) containing acidic protons may be converted into their therapeutically active non-toxic base, *i.e.* metal or amine, addition salt forms by treatment with appropriate organic and inorganic bases. Appropriate base salt forms comprise, for example, the ammonium salts, the alkali and earth alkaline metal salts, e.g. the lithium, sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, e.g. the benzathine, *N*-methyl-D-glucamine, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like.

Conversely said salt forms can be converted into the free forms by treatment with an appropriate base or acid.

The term addition salt as used hereinabove also comprises the solvates which the compounds of formula (I) as well as the salts thereof, are able to form. Such solvates are for example hydrates, alcoholates and the like.

The *N*-oxide forms of the compounds of formula (I) are meant to comprise those compounds of formula (I) wherein one or several nitrogen atoms are oxidized to the so-called *N*-oxide.

The term "stereochemically isomeric forms" as used hereinbefore and hereinafter defines all the possible stereoisomeric forms in which the compounds of formula (I) may occur. Unless otherwise mentioned or indicated, the chemical designation of compounds denotes the mixture, and in particular the racemic mixture, of all possible

stereochemically isomeric forms, said mixtures containing all diastereomers and enantiomers of the basic molecular structure. Stereochemically isomeric forms of the compounds of formula (I) and mixtures of such forms are obviously intended to be encompassed by formula (I).

In particular, the compounds of formula (I) and some of the intermediates hereinafter have at least one stereogenic center in their structure. This stereogenic center may be present in a R and a S configuration, said R and S notation is used in correspondance with the rules described in Pure Appl. Chem., 1976, *45*, 11-30.

Some of the compounds of formula (I) may also exist in their tautomeric forms. Such forms although not explicitly indicated in the above formula are intended to be included within the scope of the present invention.

Whenever used hereinafter, the term compounds of formula (I) is meant to include also the *N*-oxides, the pharmaceutically acceptable addition salts and all stereoisomeric forms.

The present compounds of formula (I) are deemed novel provided that

- when X is CH; L is a radical of formula (a) wherein B^1 is $-CH_2-$ and R^1 is pyridin-2-ylmethyl, thien-2-ylmethyl, furan-2-ylmethyl, benzyl or 4-fluorobenzyl, then $-a^1=a^2-a^3=a^4-$ is other than a -N=CH-CH=CH-; and
- when X is CH; L is a radical of formula (a) wherein B^1 is $-CH_2-$ and R^1 is 4-methoxyphenylmetyl or thiazol-4-ylmethyl, then $-a^1=a^2-a^3=a^4-$ is other than a -CH=CH-CH=CH-; and
- when X is N; L is a radical of formula (d) wherein Alk is 1,3-propanediyl, then R^4 is other than phenylamino.

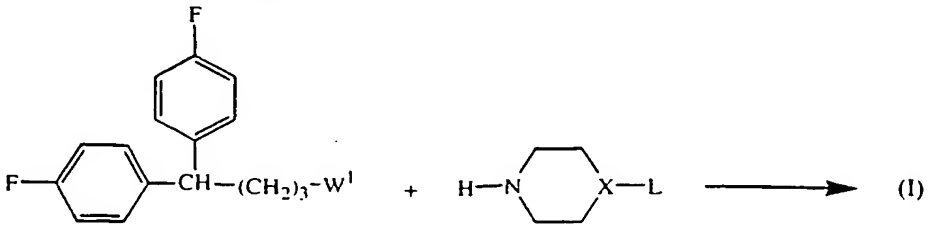
The present invention also relates to the novel compounds of formula (I) as defined hereinabove for use as a medicine.

An interesting group of compounds are those compounds of formula (I) wherein n is 0, m is 1; R^1 is C_{1-4}alkyl optionally substituted with C_{1-4}alkyloxy, arylcarbonyl or imidazo[1,2-a]pyridinyl and R^4 is thienyl, furanyl or a radical of formula (d-1).

Preferred compounds are the compounds of formula (I) wherein L is a radical of formula (a) or (b).

In general, the compounds of formula (I) can be prepared according to reaction procedures described in EP-A-0,151,826 and GB-1,055,100, more in particular, by

reacting an intermediate of formula (II) wherein W^1 is an appropriate leaving group such as, for example, a halogen, with an intermediate of formula (III).

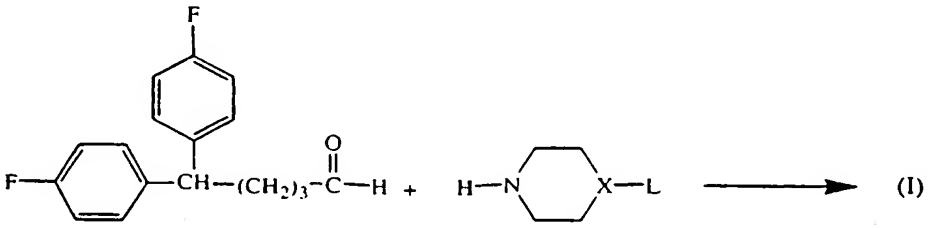


(II) (III)

Said reaction may be performed in a reaction-inert solvent such as, for example, methylisobutyl keton, *N*,*N*-dimethylacetamide or *N*,*N*-dimethylformamide, in the presence of a suitable base such as, for example, sodium carbonate, sodium bicarbonate or triethylamine, and optionally in the presence of potassium iodide.

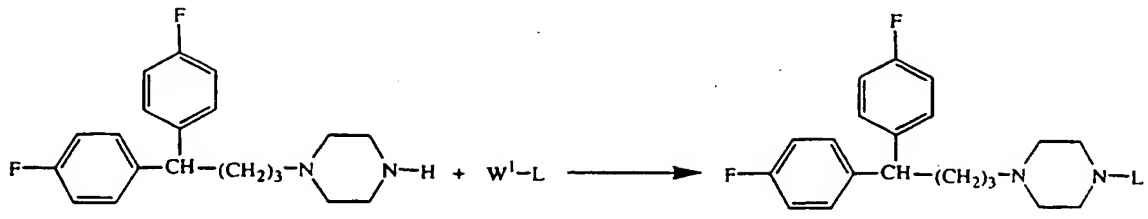
In this and the following preparations, the reaction products may be isolated from the reaction medium and, if necessary, further purified according to methodologies generally known in the art such as, for example, extraction, crystallization, distillation, trituration and chromatography.

Alternatively, the compounds of formula (I) can be prepared by reductive alkylation. An intermediate of formula (IV) is then reacted with an intermediate of formula (III) in a reaction-inert solvent such as, for example, methanol, in the presence of a reducing agent such as, for example, hydrogen in the presence of a suitable catalyst, e.g. palladium on activated charcoal, Conveniently, thiophene is added to the reaction mixture.



(IV) (III)

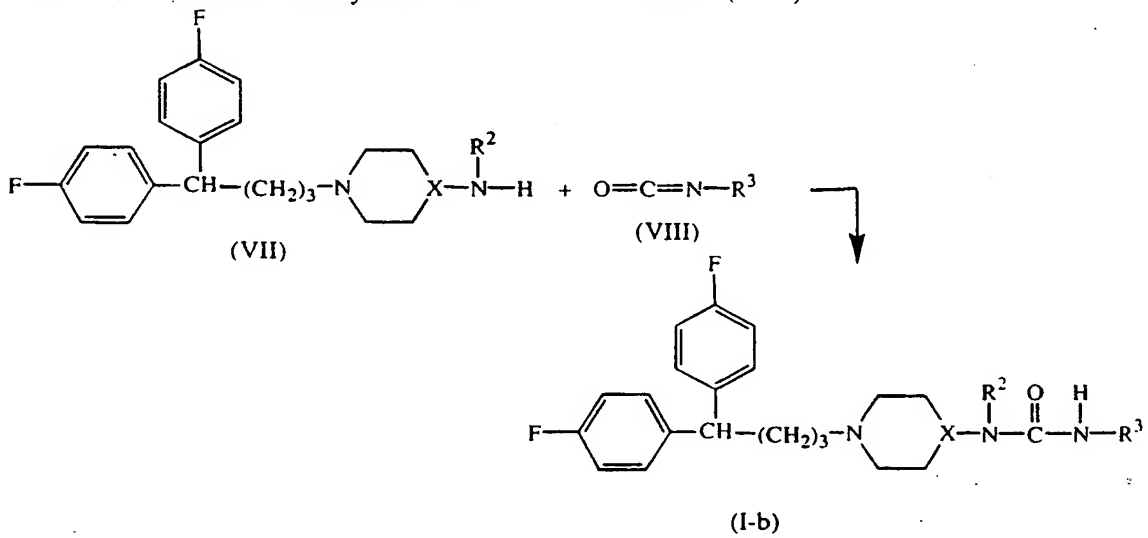
The compounds of formula (I) wherein X is N, said compounds being represented by formula (I-a), may be prepared by reacting an intermediate of formula (V) with an intermediate of formula (VI) wherein W^1 is a suitable leaving group such as for example, a halogen.



(V) (VI) (I-a)

Said reaction may be performed in a reaction-inert solvent such as, for example, methylisobutyl keton, *N*,*N*-dimethylacetamide or *N*,*N*-dimethylformamide, in the presence of a suitable base such as, for example, sodium carbonate, sodium bicarbonate or triethylamine, and optionally in the presence of potassium iodide.

The compounds of formula (I) wherein L is a radical of formula (b), said compounds being represented by formula (I-b), may be prepared by reacting an intermediate of formula (VII) with an isocyanato derivative of formula (VIII).



(VII) (VIII) (I-b)

Said reaction may be performed in a reaction-inert solvent such as, for example, diisopropylether.

The compounds of formula (I) can also be converted into each other following art-known procedures of functional group transformation.

The compounds of formula (I) may also be converted to the corresponding *N*-oxide forms following art-known procedures for converting a trivalent nitrogen into its *N*-oxide form. Said *N*-oxidation reaction may generally be carried out by reacting the starting material of formula (I) with 3-phenyl-2-(phenylsulfonyl)oxaziridine or with an appropriate organic or inorganic peroxide. Appropriate inorganic peroxides comprise, for example, hydrogen peroxide, alkali metal or earth alkaline metal peroxides, e.g.

sodium peroxide, potassium peroxide; appropriate organic peroxides may comprise peroxy acids such as, for example, benzenecarboperoxoic acid or halo substituted benzenecarboperoxoic acid, e.g. 3-chlorobenzenecarboperoxoic acid, peroxoalkanoic acids, e.g. peroxoacetic acid, alkylhydroperoxides, e.g. t-butyl hydroperoxide. Suitable solvents are, for example, water, lower alkanols, e.g. ethanol and the like, hydrocarbons, e.g. toluene, ketones, e.g. 2-butanone, halogenated hydrocarbons, e.g. dichloromethane, and mixtures of such solvents.

Some of the compounds of formula (I) and some of the intermediates in the present invention may contain an asymmetric carbon atom. Pure stereochemically isomeric forms of said compounds and said intermediates can be obtained by the application of art-known procedures. For example, diastereoisomers can be separated by physical methods such as selective crystallization or chromatographic techniques, e.g. counter current distribution, liquid chromatography and the like methods. Enantiomers can be obtained from racemic mixtures by first converting said racemic mixtures with suitable resolving agents such as, for example, chiral acids, to mixtures of diastereomeric salts or compounds; then physically separating said mixtures of diastereomeric salts or compounds by, for example, selective crystallization or chromatographic techniques, e.g. liquid chromatography and the like methods; and finally converting said separated diastereomeric salts or compounds into the corresponding enantiomers. Pure stereochemically isomeric forms may also be obtained from the pure stereochemically isomeric forms of the appropriate intermediates and starting materials, provided that the intervening reactions occur stereospecifically.

An alternative manner of separating the enantiomeric forms of the compounds of formula (I) and intermediates involves liquid chromatography, in particular liquid chromatography using a chiral stationary phase.

Some of the intermediates and starting materials are known compounds and may be commercially available or may be prepared according to art-known procedures.

Glycine is an amino acid neurotransmitter in the central and peripheral nervous system, both at inhibitory and excitatory synapses. These distinct functions of glycine are mediated by two types of receptor, each of which is associated with a different class of glycine transporter. The inhibitory actions of glycine are mediated by glycine receptors that are sensitive to the convulsant alkaloid strychnine, and are therefore referred to as 'strychnine-sensitive.' Strychnine-sensitive glycine receptors are found predominantly in the spinal cord and brainstem.

Glycine functions in excitatory transmission by modulating the actions of glutamate, the major excitatory neurotransmitter in the nervous system (Johnson and Ascher, Nature, 325, 529-531 (1987); Fletcher et al., Glycine Transmission, (Otterson and Storm-Mathisen, eds., 1990), pp. 193-219). Specifically, glycine is an obligatory co-agonist at the class of glutamate receptor termed N-methyl-D-aspartate (NMDA) receptor. NMDA receptors are widely distributed throughout the brain, with a particularly high density in the cerebral cortex and hippocampal formation.

Transporters take up neurotransmitter from the synapse, thereby regulating the concentration and term of neurotransmitter in the synapse, which together determine the magnitude of synaptic transmission. By preventing the spread of neurotransmitter to neighboring synapses, transporters maintain the fidelity of synaptic transmission. Last, by re-uptake of released transmitter into the presynaptic terminal, transporters allow for transmitter reutilization. Neurotransmitter transport is dependent on extracellular sodium and the voltage difference across the membrane. Under specific conditions, for example during a seizure, transporters can function in reverse, releasing neurotransmitter in a calciumindependent non-exocytotic manner (Attwell et al., Neuron, 11, 401-407 (1993)). Modulation of neurotransmitter transporters thus provides a means for modifying synaptic activity, which provides useful therapy for the treatment of disturbances of the central and peripheral nervous system.

Molecular cloning has revealed the existence of two classes of glycine transporters, termed GlyT-1 and GlyT-2. GlyT-1 is found predominantly in the forebrain, and its distribution corresponds to that of glutamatergic pathways and NMDA receptors (Smith, et al., Neuron. 8, 927-935 (1992)). At least three splice variants of GlyT-1 are known, namely GlyT-1a, GlyT-1b and GlyT-1c (Kim, et al., Molecular Pharmacology, 45, 608-617 (1994)), each of which displays a unique distribution in the brain and peripheral tissues. GlyT-2, in contrast, is found predominantly in the brainstem and spinal cord, and its distribution corresponds closely to that of strychnine-sensitive glycine receptors (Liu et al., J Biological Chemistry., 268,. 22802-22808 (1993); Jursky and Nelson, Neurochemistry, 64, 10261033 (1995)). Thus, one can expect that by regulating the synaptic levels of glycine, GlyT-1 and GlyT-2 selectively modulate the activity of NMDA receptors and strychnine-sensitive glycine receptors, respectively.

Compounds that inhibit or activate glycine transporters would thus be expected to alter receptor function, and provide therapeutic benefits in a variety of disease states. Thus, inhibition of GlyT-2 could be used to diminish the activity of neurons having

strychnine-sensitive glycine receptors via increasing synaptic levels of glycine, and so diminish the transmission of pain-related (i.e., nociceptive) information in the spinal cord, which has been shown to be mediated by these receptors. Yaksh, Pain, 37, 111-123 (1989). Additionally, enhancing inhibitory glycinergic transmission through strychnine-sensitive glycine receptors in the spinal cord can be used to decrease muscle hyperactivity, which is useful in treating diseases or conditions associated with increased muscle contraction, such as spasticity, myoclonus, and epilepsy (Truong et al., Movement Disorders, 3 , 77-87 (1988); Becker, FASEB J, 4 2767-2774 (1990)). Spasticity that can be treated via modulation of glycine receptors is associated with epilepsy, stroke, head trauma, multiple sclerosis, spinal cord injury, dystonia, and other conditions of illness and injury of the nervous system.

NMDA receptors are involved in memory and learning (Rison and Stanton, Neurosci. Biobehav. Rev., 19, 533 552 (1995); Danysz at al., Behavioral Pharmacol., 6, 455-474 (1995)); and decreased function of NMDA-mediated neurotransmission appears to contribute to the symptoms of schizophrenia (Olney and Farber, Archives General Psychiatry, 52, 998-1007 (1996). Thus, agents that inhibit GlyT-1 and thereby increase glycine activation of NMDA receptors can be used as novel antipsychotics and anti-dementia agents, and to treat other diseases in which cognitive processes are impaired, such as attention deficit disorders and organic brain syndromes. Conversely, over-activation of NMDA receptors has been implicated in a number of disease states, in particular the neuronal death associated with stroke, head trauma and possibly neurodegenerative diseases, such as Alzheimer's disease, multi-infarct dementia, AIDS dementia, Huntington's disease, Parkinson's disease, amyotrophic lateral sclerosis or other conditions in which neuronal cell death occurs. Coyle & Puttfarcken, Science, 262, 689-695 (1993); Lipton and Rosenberg, New Engl. J. of Medicine, 330, 613-622 (1993); Choi, Neuron 1, 623-634 (1988). Thus, pharmacological agents that increase the activity of GlyT-1 will result in decreased glycine-activation of NMDA receptors, which activity can be used to treat these and related disease states. Similarly, drugs that directly block the glycine site on the NMDA receptors can be used to treat these and related disease states.

For administration purposes, the subject compounds may be formulated into various pharmaceutical compositions comprising a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amount of a novel compound of formula (I). To prepare the pharmaceutical compositions of this invention, an effective amount of the particular compound, in addition salt or in free acid or base form, as the active

ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirably in unitary dosage form suitable, preferably, for administration orally, percutaneously, or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs and solutions; or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable solutions containing compounds of formula (I) may be formulated in an oil for prolonged action. Appropriate oils for this purpose are, for example, peanut oil, sesame oil, cottonseed oil, corn oil, soy bean oil, synthetic glycerol esters of long chain fatty acids and mixtures of these and other oils. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wettable agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not cause any significant deleterious effects on the skin. Said additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions. These compositions may be administered in various ways, e.g., as a transdermal patch, as a spot-on or as an ointment. Addition salts of (I) due to their increased water solubility over the corresponding free base or free acid form, are obviously more suitable in the preparation of aqueous compositions.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used in the specification and claims herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect, in association with the required pharmaceutical carrier. Examples of such dosage unit forms are

tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

The following examples are intended to illustrate the present invention.

Experimental part

Example A.1

A mixture of 1-chloro-4,4-bis(4-fluorophenyl)butane (5.6 g), 4-(1,2,3,4-tetrahydro-2-oxo-3-quinazolinyl)piperidine (3.5 g), sodium carbonate (6.36 g), a few crystals of KI in methylisobutyl keton (160 ml) was stirred and refluxed for 2 days. After cooling water was added (250 ml). The separated organic layer was dried, filtered and the solvent evaporated. The residue was recrystallized from methylisobutyl keton (80 ml), yielding 3g of 3-[1-[4,4-bis(4-fluoromethyl)butyl]-4-piperidinyl]-3,4-dihydro-2(1*H*)-quinazolinone; mp. 199-200.5 °C (compound 1).

Analogously were prepared :

4-[2-[1-[4,4-bis(4-fluorophenyl)butyl]-4-piperidinyl]acetyl]-3,4-dihydro-3-phenyl-2(1*H*)-quinoxalinone ethanedioate(1:1); mp. 190.8°C (compound 2);

N-[1-[4,4-bis(4-fluorophenyl)butyl]-4-piperidinyl]-1-(imidazo[1,2-a]pyridin-2-ylmethyl)-1*H*-benzimidazol-2-amine; mp. 160.1°C (compound 3);

2-[[4-[4,4-bis(4-fluorophenyl)butyl]-1-piperazinyl]methyl]-3-(2-ethoxyethyl)-3*H*-imidazo[4,5-b]pyridine ethanedioate (1:2); mp. 173.2°C (compound 4);

3-[1-[4,4-bis(4-fluoromethyl)butyl]-4-piperidinyl]-3,4-dihydro-pyrido[2,3-d]-2(1*H*)-pyrimidinone dihydrochloride; mp. 220-222°C (compound 5).

Example A.2

A mixture of 4-fluoro-γ-(4-fluorophenyl)benzenebutanal (2.6 g), 1-(4-fluorophenyl)-3-[2-(4-piperidinylmethyl)-1*H*-benzimidazol-1-yl]-1-propanone dihydrobromide monohydrate (5.5 g), a solution of thiophene in ethanol 3% (1 g), potassium acetate (3 g) and methanol (200 ml) was hydrogenated at normal pressure and at 50°C with palladium-on-charcoal catalyst 10% (2 g). After the calculated amount of hydrogen was taken up, the catalyst was filtered off and the filtrate was evaporated. Water was added to the oily residue and the whole was alkalized with ammonium hydroxide. The product was extracted with 4-methyl-2-pentanone. The extract was dried, filtered and evaporated. The oily residue was purified by column chromatography over silica gel using a mixture of trichloromethane and methanol (95:5 by volume) as eluent. The oily residue was converted into the ethanedioate salt in acetonitrile and 4-methyl-2-pentanone. The salt was allowed to crystallize. The product was filtered off and dried,

yielding 5 g (63.3 %) of 3-[2-[[1-[4,4-bis(4-fluorophenyl)butyl]-4-piperidinyl]methyl]-1*H*-benzimidazol-1-yl]-1-(4-fluorophenyl)-1-propanone ethanedioate (1:2); mp. 156.4°C (compound 6).

Example A.3

A mixture of 1-[4,4-bis(4-fluorophenyl]butyl]-piperazine (6.9 g), 4-chloro-1-(2-thienyl)-butanone (4,1 g), sodium carbonate (3.18 g), a few crystals of potassium iodide in 4-methyl-2-pentanone (200 ml) was refluxed for 24 hours. Then a second portion of 4-chloro-1-(2-thienyl)butanone (4.1 g) was added and the whole was stirred and refluxed for an additional 36 hours. After cooling, water was added (100 ml). The organic layer was separated, dried over potassium carbonate, filtered and evaporated. The oily residue was dissolved in anhydrous ether (480 ml). The solution was filtered and gaseous hydrogen chloride was introduced into the filtrate. The precipitated salt was filtered off and crystallized from 2-propanol (320 ml), yielding 4-[4,4-bis(4-fluorophenyl)butyl]-1-piperazinyl]-1-(2-thienyl)butanone; mp. 227.5-230°C (compound 7).

Example A.4

To a stirred solution of 1-[4,4-bis(4-fluorophenyl)butyl]-*N*-(4-methoxyphenyl)-4-piperidinamine (6.75g) in 2,2'-oxybispropane (105 ml) and tetrahydrofuran (45 ml) was added dropwise a solution of 2-isocyanatopropane (1.36 g) in 2,2'-oxybispropane (35 ml). Upon completion, stirring was continued first for 1 day at room temperature and further for 1 hour at about 50°C. The reaction mixture was evaporated and the residue was crystallized from a mixture of 2,2'-oxybispropane and 2-propanol, yielding *N*-[1-[4,4-bis(4-fluorophenyl)butyl]-4-piperidinyl]-*N*-(4-methoxyphenyl)-*N*'-(1-methylethyl)urea (4.8 g, 59%); mp. 170.9°C (compound 8).

Analogously were prepared :

N-[1-[4,4-bis(4-fluorophenyl)butyl]-4-piperidinyl]-*N*'-butyl-*N*-(4-methoxyphenyl)urea; mp. 101.9°C (compound 9);

N-[1-[4,4-bis(4-fluorophenyl)butyl]-4-piperidinyl]-*N*-(4-methoxyphenyl)-*N*'-propylurea; mp. 124.1°C (compound 10);

N-[1-[4,4-bis(4-fluorophenyl)butyl]-4-piperidinyl]-*N*'-cyclohexyl-N-(4-methoxyphenyl)urea; mp. 128.2°C (compound 11);

N-[1-[4,4-bis(4-fluorophenyl)butyl]-4-piperidinyl]-*N*'-ethyl-*N*-(4-methylphenyl)urea; mp. 129.1°C (compound 12);

N-[1-[4,4-bis(4-fluorophenyl)butyl]-4-piperidinyl]-*N*'-(1-methylethyl)-*N*-(4-methylphenyl)urea; mp. 167.2°C (compound 13); and

N-[1-[4,4-bis(4-fluorophenyl)butyl]-4-piperidinyl]-*N*'-(4-chlorophenyl)-*N*'-(1-methylethyl)urea; mp. 157.4°C (compound 14).

Pharmacological example

Example B.1: Assay of transport via GlyT1 transporters

Subconfluent HEK 293 -GlyT1 cells (*i.e.* a cell line which stably expresses human glycine transporter 1) were seeded in Cytostar-T plates at a concentration of 50,000 cells per well in 100 µl DMEM medium (Dulbecco's Modified Eagle Medium supplemented with 10% foetal bovine serum, 1 mM Na-pyruvate, 2 mM glutamine, 100 U penicillin/ml and 0.1 mg/ml streptomycin). The cells were incubated for 48 hours at 37°C, 5% CO_2, 95% humidity.

On day 3, the cells were washed using a Tecan PW96 microprocessor controlled washer designed to wash all 96 wells of a microplate simultaneously with uptake buffer (25 mM Hepes, 5.4 mM K-gluconate, 1.8 mM Ca-gluconate, 0.8 mM $MgSO_4$, 140 mM NaCl, 5 mM glucose, 5 mM alanine, adjusted to pH 7.5 with 2M Tris). The Tecan PW96 was programmed to wash the cells five times leaving 75 µl in each well. The test compounds were dissolved at different concentrations in the micromolar range in DMSO. 1 µl Test solution was added to each well and the cells were incubated for 5' to 10' at ambient temperature. Then there was added 25 µl 30 µM [$U^{14}C$]glycine diluted in uptake buffer. The cells were incubated for 1 hour at ambient temperature. The plates were then sealed and [$U^{14}C$]glycine uptake was determined on a Packard microplate scintillation counter (TopCount). From the results obtained for the various concentrations of each test drug, the concentration giving 50 % inhibition (IC_{50}) of glycine uptake was calculated. Calculated data for the test compounds according to the instant invention are shown in table 1 as pIC_{50} values (negative log values of the IC_{50}).

Comp. 15 being 2-[[1-[4,4-bis(4-fluorophenyl)butyl]-4-piperidinyl]methyl]-3-(2-pyridinylmethyl)-3*H*-imidazo[4,5-b]pyridine ethanedioate (1:2);
comp. 16 being 2-[[1-[4,4-bis(4-fluorophenyl)butyl]-4-piperidinyl]methyl]-3-[(4-fluorphenyl)methyl]-3*H*-imidazo[4,5-b]pyridine ethanedioate (1:2);
comp. 17 being 2-[[1-[4,4-bis(4-fluorophenyl)butyl]-4-piperidinyl]methyl]-3-(phenylmethyl)-3*H*-imidazo[4,5-b]pyridine ethanedioate (1:2);
comp. 18 being 2-[[1-[4,4-bis(4-fluorophenyl)butyl]-4-piperidinyl]methyl]-3-(2-thienylmethyl)-3*H*-imidazo[4,5-b]pyridine ethanedioate (1:1);
comp. 19 being 2-[[1-[4,4-bis(4-fluorophenyl)butyl]-4-piperidinyl]methyl]-3-(2-furanylmethyl)-3*H*-imidazo[4,5-b]pyridine ethanedioate (1:2);
comp. 20 being 2-[[1-[4,4-bis(4-fluorophenyl)butyl]-4-piperidinyl]methyl]-3-[(4-methoxy-phenyl)methyl]-1*H*-benzimidazole ethanedioate (1:2);
comp. 21 being 2-[[1-[4,4-bis(4-fluorophenyl)butyl]-4-piperidinyl]methyl]-3-

(4-thiazolyl-methyl)-1*H*-benzimidazole ethanedioate (1:2); as disclosed in EP-A-0,151,826;

and comp. 22 being 1-[4,4-di(4-fluorophenyl)butyl]-4-[3-(anilinocarbonyl)-propyl]-piperazine dihydrochloride as disclosed in GB-1,055,100, were also tested.

Table 1

Comp No.	pIC_{50}
1	6.61
2	6.34
3	6.14
4	6.81
5	6.26
6	6.44
7	6.29
8	6.51

Comp No.	pIC_{50}
9	6.15
10	6.12
11	6.28
12	6.02
13	6.18
14	6.18
15	6.65
16	6.55

Comp No.	pIC_{50}
17	6.42
18	6.26
19	6.15
20	6.09
21	6.07
22	6.33

C. Composition examples

The following formulations exemplify typical pharmaceutical compositions suitable for systemic administration to animal and human subjects in accordance with the present invention.

"Active ingredient" (A.I.) as used throughout these examples relates to a compound of formula (I) or a pharmaceutically acceptable addition salt thereof.

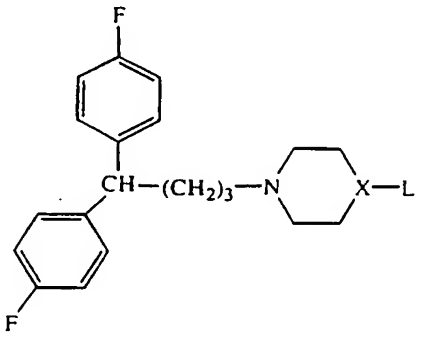
Example C.1 : film-coated tablets

Preparation of tablet core A mixture of 100 g of the A.I., 570 g lactose and 200 g starch was mixed well and thereafter humidified with a solution of 5 g sodium dodecyl sulfate and 10 g polyvinylpyrrolidone in about 200 ml of water. The wet powder mixture was sieved, dried and sieved again. Then there was added 100 g microcrystalline cellulose and 15 g hydrogenated vegetable oil. The whole was mixed well and compressed into tablets, giving 10.000 tablets, each comprising 10 mg of the active ingredient.

Coating To a solution of 10 g methyl cellulose in 75 ml of denaturated ethanol there was added a solution of 5 g of ethyl cellulose in 150 ml of dichloromethane. Then there were added 75 ml of dichloromethane and 2.5 ml 1,2,3-propanetriol. 10 g of polyethylene glycol was molten and dissolved in 75 ml of dichloromethane. The latter solution was added to the former and then there were added 2.5 g of magnesium octadecanoate, 5 g of polyvinylpyrrolidone and 30 ml of concentrated color suspension and the whole was homogenated. The tablet cores were coated with the thus obtained mixture in a coating apparatus.

Claims

1. The use of a glycine transport inhibiting compound for the preparation of a medicament for treating disorders of the central and peripheral nervous system, said compound having the formula

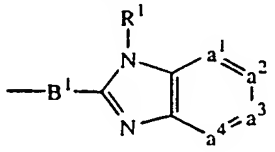


(I)

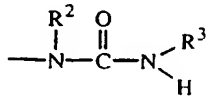
a *N*-oxide, a stereochemically isomeric form or a pharmaceutically acceptable addition salt thereof, wherein

X represents CH or N;

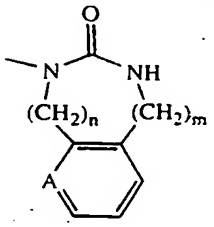
L represents a radical of formula



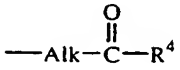
(a)



(b)



(c)



(d)

wherein n is 0 or 1;

m is 0 or 1;

Alk represents C_{1-6}alkanediyl;

A represents N or CH;

B^1 represents CH_2 or NH;

$-a^1=a^2-a^3=a^4-$ represents a bivalent radical of formula

-CH=CH-CH=CH- (a-1); or

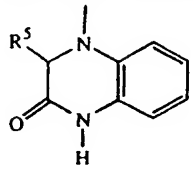
-N=CH-CH=CH- (a-2);

R^1 represents C_{1-4}alkyl optionally substituted with C_{1-4}alkyloxy, pyridinyl, aryl, arylcarbonyl, thienyl, furanyl, imidazo[1,2-a]pyridinyl, thiazolyl;

R^2 represents hydrogen or aryl;

R^3 represents hydrogen, C_{1-6}alkyl or C_{3-7}cycloalkyl;

R^4 represents thienyl, furanyl, arylamino or a radical of formula



(d-1)

wherein R^5 is hydrogen or aryl;

aryl represents phenyl optionally substituted with 1 or 2 substituents selected from C_{1-4}alkyl, halo, hydroxy, C_{1-4}alkyloxy.

2. The use according to claim 1 wherein L is a radical of formula (a) or (b).

3. The use according to claim 1 wherein the disorder is psychoses, pain, epilepsy, a neurodegenerative diseases, stroke, head trauma or multiple sclerosis.

4. A compound of formula (I) as defined in claims 1 or 2 provided that

- when X is CH; L is a radical of formula (a) wherein B^1 is $-CH_2-$ and R^1 is pyridin-2-ylmethyl, thien-2-ylmethyl, furan-2-ylmethyl, benzyl or 4-fluorobenzyl, then $-a^1=a^2-a^3=a^4-$ is other than a -N=CH-CH=CH-; and
- when X is CH; L is a radical of formula (a) wherein B^1 is $-CH_2-$ and R^1 is 4-methoxyphenylmetyl or thiazol-4-ylmethyl, then $-a^1=a^2-a^3=a^4-$ is other than a -CH=CH-CH=CH-; and
- when X is N; L is a radical of formula (d) wherein Alk is 1,3-propanediyl, then R^4 is other than phenylamino.

5. A compound as claimed in claim 4 wherein n is 0, m is 1; R^1 is C_{1-4}alkyl optionally substituted with C_{1-4}alkyloxy, arylcarbonyl or imidazo[1,2-a]pyridinyl and R^4 is thienyl, furanyl or a radical of formula (d-1).

6. A compound as claimed in claim 4 wherein the compound is
3-[1-[4,4-bis(4-fluoromethyl)butyl]-4-piperidinyl]-3,4-dihydro-2(1*H*)-quinazolinone;
4-[2-[1-[4,4-bis(4-fluorophenyl)butyl]-4-piperidinyl]acetyl]-3,4-dihydro-3-phenyl-2(1*H*)-quinoxalinone;
N-[1-[4,4-bis(4-fluorophenyl)butyl]-4-piperidinyl]-1-(imidazo[1,2-a]pyridin-2-yl-methyl)-1*H*-benzimidazol-2-amine;
2-[[4-[4,4-bis(4-fluorophenyl)butyl]-1-piperazinyl]methyl]-3-(2-ethoxyethyl)-3*H*-imidazo[4,5-b]pyridine;
3-[1-[4,4-bis(4-fluoromethyl)butyl]-4-piperidinyl]-3,4-dihydro-pyrido[2,3-d]-2(1*H*)-pyrimidinone;

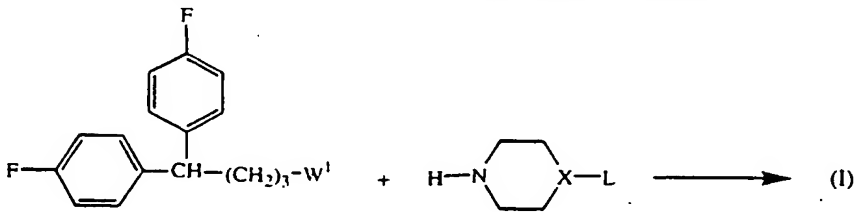
3-[2-[[1-[4,4-bis(4-fluorophenyl)butyl]-4-piperidinyl]methyl]-1*H*-benzimidazol-1-yl]-1-(4-fluorophenyl)-1-propanone;
4-[4,4-bis(4-fluorophenyl)butyl]-1-piperazinyl]-1-(2-thienyl)butanone;
N-[1-[4,4-bis(4-fluorophenyl)butyl]-4-piperidinyl]-*N*-(4-methoxyphenyl)-*N*'-(1-methylethyl)urea;
N-[1-[4,4-bis(4-fluorophenyl)butyl]-4-piperidinyl]-*N*'-butyl-*N*-(4-methoxyphenyl)urea;
N-[1-[4,4-bis(4-fluorophenyl)butyl]-4-piperidinyl]-*N*-(4-methoxyphenyl)-*N*'-propylurea;
N-[1-[4,4-bis(4-fluorophenyl)butyl]-4-piperidinyl]-*N*'-cyclohexyl-N-(4-methoxyphenyl)urea;
N-[1-[4,4-bis(4-fluorophenyl)butyl]-4-piperidinyl]-*N*'-ethyl-*N*-(4-methylphenyl)urea;
N-[1-[4,4-bis(4-fluorophenyl)butyl]-4-piperidinyl]-*N*'-(1-methylethyl)-*N*-(4-methylphenyl)urea; or
N-[1-[4,4-bis(4-fluorophenyl)butyl]-4-piperidinyl]-*N*'-(4-chlorophenyl)-*N*'-(1-methylethyl)urea; a *N*-oxide, a stereochemically isomeric form or a pharmaceutically acceptable addition salt thereof

7. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and as active ingredient a therapeutically effective amount of a compound as described in any one of claims 4 to 6.

8. A process of preparing a pharmaceutical composition as claimed in claim 7, characterized in that, a therapeutically effective amount of a compound as claimed in any one of claims 4 to 6 is intimately mixed with a pharmaceutical carrier.

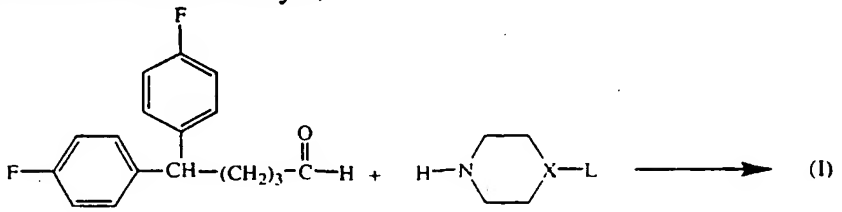
9. A compound as described in any one of claims 4 to 6 for use as a medicine.

10. A process of preparing a compound as described in claim 4, characterized by,
a) by reacting an intermediate of formula (II) wherein W^1 is an appropriate leaving group with an intermediate of formula (III) in a reaction-inert solvent, in the presence of a suitable base and optionally in the presence of potassium iodide;



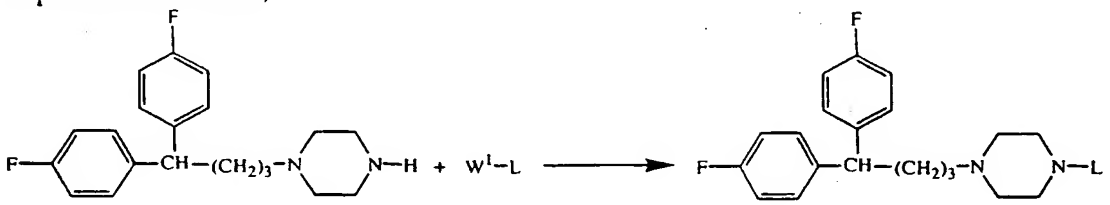
(II) (III)

b) by reductive alkylationof an intermediate of formula (III) with an intermediate of formula (IV) in a reaction-inert solvent, in the presence of a reducing agent optionally in the presence of a suitable catalyst;



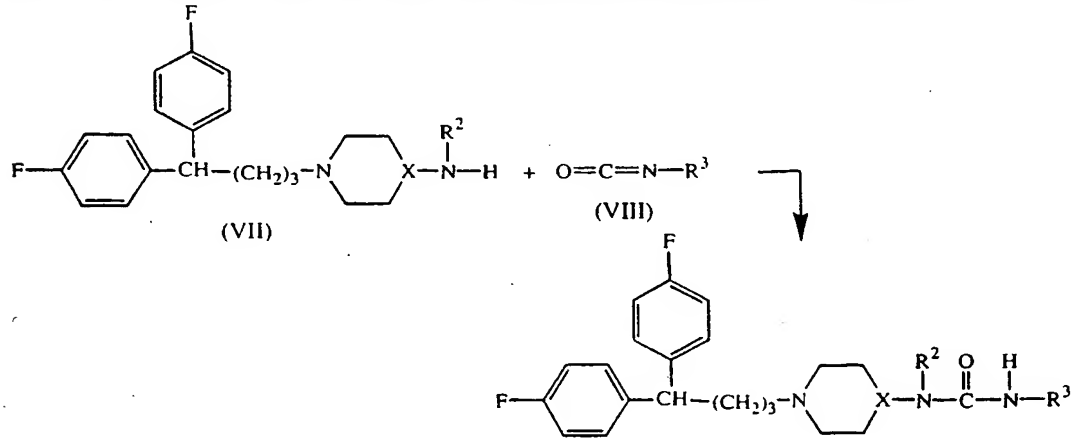
(IV) (III) (I)

c) by reacting an intermediate of formula (V) with an intermediate of formula (VI) wherein W^1 is a suitable leaving group; thus forming a compound of formula (I-a), in a reaction-inert solvent, in the presence of a suitable base and optionally in the presence of potassium iodide;



(V) (VI) (I-a)

d) by reacting an intermediate of formula (VII) with an isocyanato derivative of formula (VIII) in a reaction-inert solvent; thus forming a compound of formula (I-b)



(VII) (VIII) (I-b)

and, if desired, converting the compounds of formula (I), into an acid addition salt by treatment with an acid, or into a base addition salt by treatment with a base, or conversely, converting the acid addition salt form into the free base by treatment with alkali, or converting the base addition salt into the free acid by treatment with acid; and, if desired, preparing *N*-oxide and/or stereochemically isomeric forms thereof.

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(54) Title: GLYCINE TRANSPORT INHIBITORS

(57) Abstract

The present invention is concerned with the use of glycine transport inhibiting [4,4–bis(4–fluorophenyl)butyl]–1–(piperazinyl and piperidinyl) derivatives for the preparation of medicaments for treating disorders of the central and peripheral nervous system, in particular psychoses, pain, epilepsy, neurodegenerative diseases (Alzheimer's disease), stroke, head trauma, multiple sclerosis and the like. The invention further comprises novel compounds, their preparation and their pharmaceutical forms.

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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/445 A61K31/495 C07D401/04 C07D401/06 C07D471/04
C07D333/22 C07D211/58
//(C07D471/04,235:00,221:00),(C07D471/04,239:00,221:00)
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	L. MCCOY ET AL.: "Chronic antipsychotic treatment alters glycine-stimulated NMDA receptor binding in rat brain" NEUROSCIENCE LETTERS, vol. 213, no. 2, 1996, pages 137-141, XP002113099 see the whole document ---	1-3
E	WO 99 25353 A (MERCK SHARP & DOHME LIMITED) 27 May 1999 see page 36, line 2 - line 8 --- -/--	1-3

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 August 1999	10. 12. 99

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	THEUNS, H

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inte ional Application No
PCT/EP 99/01309

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JANSSENS ET AL: "New antihistaminic N-heterocyclic 4-piperidinamines. 3. Synthesis and antihistaminic activity of N-(4-piperidinyl)-3H-imidazo[4,5 -b]pyridin-2- amines" JOURNAL OF MEDICINAL CHEMISTRY, vol. 28, 1985, pages 1943-1947, XP002104126 see abstract line 8 ---	1-4,6-10
X	JANSSENS F ET AL: "NEW ANTIHISTAMINIC N-HETEROCYCLIC 4-PIPERIDINAMINES. 1. SYNTHESIS AND ANTIHISTAMINIC ACTIVITY OF N-(4-PIPERIDINYL)-1H-BENZIMIDAZOL-2 -AMINES" JOURNAL OF MEDICINAL CHEMISTRY, vol. 28, no. 12, 1 January 1985, pages 1925-1933, XP002074741 see abstract line 8 ---	1-4,6-10
X	EP 0 151 826 A (JANSSEN PHARMACEUTICA N.V.) 21 August 1985 cited in the application see page 116, line 1 - line 5 ---	1-4,6-10
X	US 4 695 575 A (JANSSENS ET AL.) 22 September 1987 see column 101 - line 5 ---	1-4,6-10
X	US 4 219 559 A (JANSSENS ET AL.) 26 August 1980 see column 11, line 61 - line 68 ---	1-4,6-10
X	EP 0 005 318 A (JANSSEN PHARMACEUTICA N.V.) 14 November 1979 see page 20, line 5 - line 8 -----	1-4,6-10

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mational application No.
PCT/EP 99/01309

B x I Observations where certain laims were found unsearchable (C ntinuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. Claims: 1-4, 6-10 (partially)
2. Claims: 1-4, 6-10 (partially)
3. Claims: 1-4 (partially)
4. Claims: 1-4, 6-10 (partially)
5. Claims: 5, and partially 4, 6-10

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-4, 6-10 (partially)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest

☐ No protest accompanied the payment of additional search fees

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 1-4, 6-10 (partially)

Use of known compounds of formula I wherein L represents a radical of formula (a). Novel compounds of this formula.

2. Claims: 1-4, 6-10 (partially)

Use of known compounds of formula I wherein L represents a radical of formula (b). Novel compounds of this formula.

3. Claims: 1-4 (partially)

Use of known compounds of formula I wherein L represents a radical of formula (c).

4. Claims: 1-4, 6-10 (partially)

Use of known compounds of formula I wherein L represents a radical of formula (d). Novel compounds of this formula.

5. Claims: 5, and partially 4, 6-10

Novel compounds of formula I wherein L represents a radical of formula (c).

INTERNATIONAL SEARCH REPORT

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